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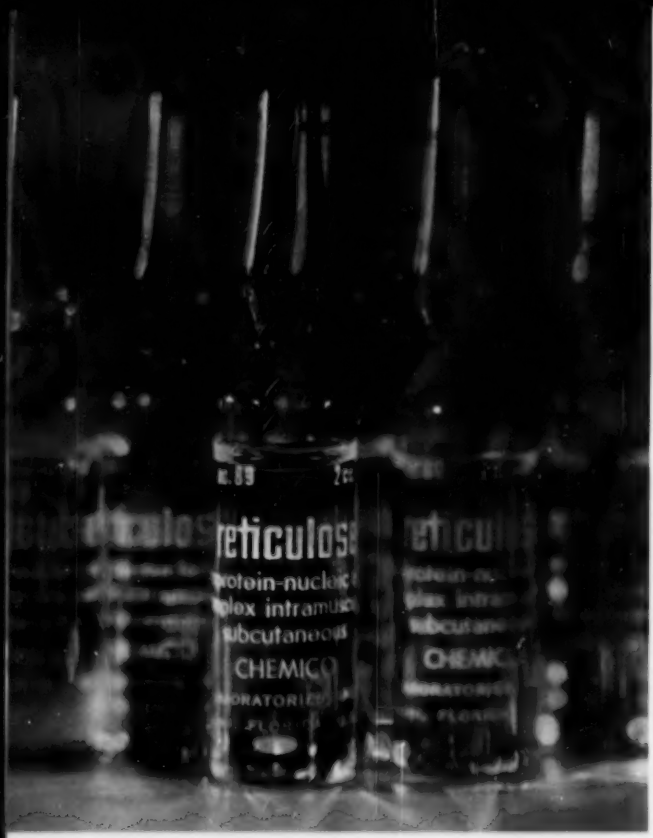

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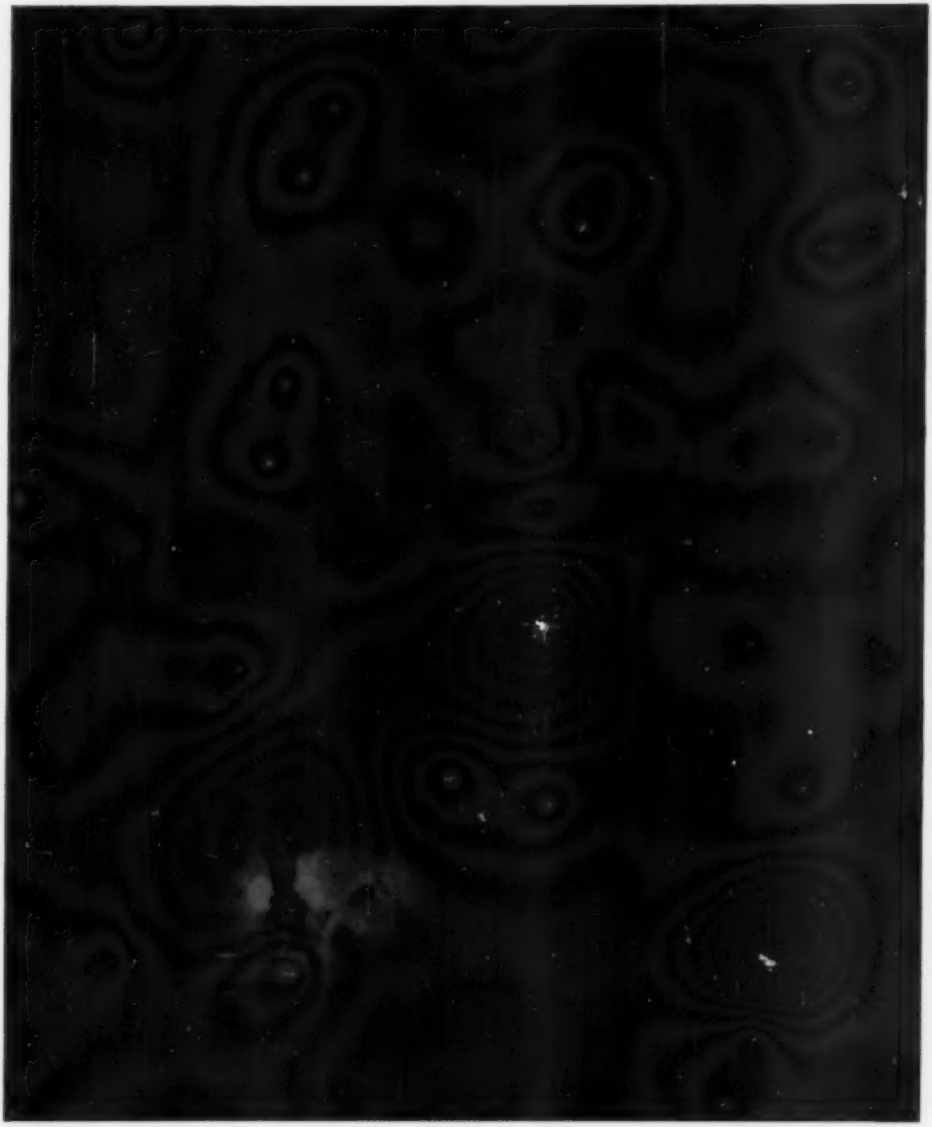

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ALBRO C. GAYLOR, *Publisher*
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CONTENTS

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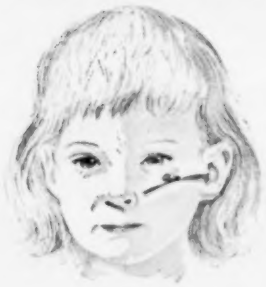

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EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, N. Y.

Phenylketonuria

A CASE REPORT OF JEWISH ANCESTRY

WILLARD R. CENTERWALL, M.D.*
CHARLES A. NEFF, M.D.**
California

PHENYLKETONURIA (PKU), also known as phenylpyruvic oligophrenia and as Fölling's Disease, is an inherited disease of mental deficiency which has been known and extensively studied for more than a quarter of a century.[1] Patient material for study has been adequate because PKU is found in one-fourth to two per cent of institutionalized mental defectives.[2,3] Although world-wide in distribution, PKU appears to occur more commonly in certain groups of peoples such as Irish, Italian, Slavic and Nordic[2] and to be extremely rare in some, such as Jewish[4] and Negro.[5,6]

In recent years increased attention has been given in the medical literature to this inherited disorder of phenylalanine metabolism, mainly because the associated mental deficiency has been found to be preventable provided the diagnosis is made early in infancy and a diet low in phenylalanine initiated.[7,8,9] Fortunately the diagnosis can be made very early, even before the onset of mental retardation, by means of exceptionally simple urine tests,[10,11,12] and can be unequivocally confirmed by a serum phenylalanine determination. These points, the ease of diagnosis, and the opportunity to prevent mental retardation have encouraged increased efforts to detect young infants with phenylketonuria both among the siblings of known cases[13] and in well baby populations.[10,11,12]

We believe it is of value to report this family for the following reasons: To our knowledge, PKU in children of Jewish ancestry has been reported only once before in the world's medical literature.[4] It is possible, therefore, that the presence of Jewish ancestry might lull suspicions of phenylketonuria and lead to a costly delay in diagnosis. Some of the problems and the methods used in the detection of PKU are well demonstrated. The involved children serve as good teaching examples of the clinical course and features typical of this disease.

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**Acting Assistant Superintendent, Porterville State Hospital, Porterville, Cal.

This study is a part of a larger research effort which is supported by grants from the National Institutes of Health (M2323), the Alumni Research Foundation of the College of Medical Evangelists, and Mead Johnson & Co.

CASE HISTORIES

Case 1—The diagnosis of PKU was made on this six-year-old girl upon admission to a large state hospital* for the mentally retarded. On admission physical examination it was noted that this little Caucasian girl had rather colorless, faded brown hair, transparent pink skin, and blue-grey eyes. She was 43 inches tall (fifth percentile for her age), weighed 41 pounds (50th percentile for her height) and had a head circumference of 18½ inches (first percentile for her height). She was wearing a diaper which had a distinct odor of phenylacetate. A drop of 10 per cent aqueous ferric chloride solution on the wet diaper gave an immediate dark green spot which faded within a few minutes. A test tube test with urine and ferric chloride further corroborated the diagnosis of phenylketonuria. Her serum phenylalanine level was 24.9 mg/100 ml. (normal 1-3 mg./100 ml.).

It was noted that she seemed irritable and unhappy, cried a great deal, and sat on the floor and played in a rather aimless, babyish way. She was spoon-fed and needed help in brushing her teeth. She was not toilet trained. An EEG was reported as "abnormal consistent with brain damage, convulsion susceptibility and drowsiness." Her developmental quotient (D.Q.) tested at 28.

Past history revealed that the pregnancy, labor, delivery, and early infancy were uneventful. Birth weight was 5 pounds. Developmental progress soon slowed, however, and she was not sitting alone until 10 months and not walking alone until three and one-half years. During her first year she refused solids and would take only milk. She had an itchy antecubital and popliteal eczema off and on between three and five years of age. The mother also had frequently noticed a peculiar, musty odor about this girl's diapers and bedding. The parents seriously began to suspect mental retardation when she was one year old.

When she was four years old the parents made application for her placement in one of the state hospitals* for the mentally retarded. In preparation for such a placement she received a preadmission examination at another center. For this occasion the parents had been instructed to collect and bring along a urine specimen from their daughter (for a routine test-tube test for PKU). The effort of collecting a urine specimen from this untrained, retarded girl was unrewarded, so when the parents showed up without the urine specimen, this part of her examination was omitted and the parents were requested to collect and mail in a urine speci-

* Porterville State Hospital, Porterville, California

men. This was done some days later, according to the parents. No preservative was advised or used. There is no record of receipt of the specimen at the center.

The family history revealed that this girl was the second of three children by this couple. A letter was sent to the parents informing them of the diagnosis of PKU in their institutionalized daughter and advising that the remaining two children at home and any subsequent offspring be tested for PKU. The parents immediately responded, and an intelligent, normal seven and one-half-year-old, blue-eyed brother and an obviously retarded 13½-month-old sister (Case No. 2) were brought in for testing.

CASE 2

When the two siblings of the child in Case 1 were tested for PKU, the seven and one-half-year-old brother's test was normal, but the younger 13½-month-old sister was found to have a positive diaper test.[14] The diagnosis of PKU was confirmed by a serum phenylalanine level of 13.7 mg./100 ml.

This little girl had a developmental history almost identical to that of her older retarded sister. Birth weight was 5 pounds, 5 ounces. She had smiled responsively at one month and was following with her eyes at two to three months. She cut her first teeth at six months and was putting things in her mouth at about this age. She sat without support at 10 months. From time to time she was noted to make herself rigid and to shake (probably not true convulsions).

Examination at 13½ months revealed an obviously retarded, very blond, fair-skinned, blue-eyed little girl who was 29¼ inches tall (55th percentile for her age), weighed 19½ pounds (15th percentile for her height) and had a head circumference of 16½ inches (first percentile for her height). She rolled over and rocked on her hands and knees, but she could not crawl, bring herself to a sitting or standing position, support her weight well on her legs, or say any words. Occasionally she looked at her hands, made scratching movements, and reached timidly for objects which she would mouth and transfer from one hand to the other but not very actively. She had a D.Q. of 38 by the Gesell Developmental Scale. An electroencephalogram was reported as normal. The parents realized that she was retarded but until recently had blamed her slowness on a turning in of the eyes which had been present since one month of age.

Before she suspected that this youngest child was retarded, the mother had noted the musty odor of the child. She worried about it because this had been present with the older retarded sister

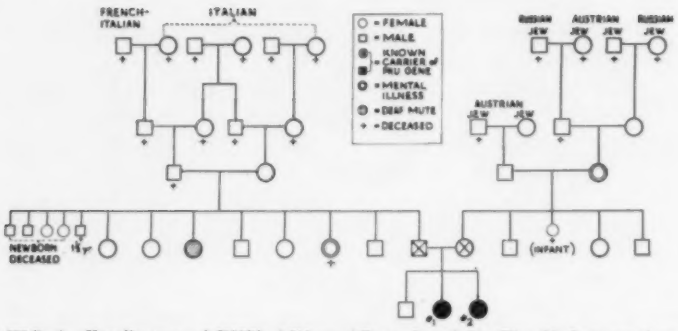

FIG. 1—Family tree of PKU children (Cases 1 and 2). The 31 first cousins are not shown on the graph, but blue eyes are common among the first cousins on both sides of the family. Thus, the blue eyes in these PKU children cannot necessarily be attributed to their disease. French-Italian means a mixture of French and Italian. Russian Jew and Austrian Jew refers to the countries in which these Jewish people lived. Unfortunate for genetic mapping, there were no relatives outside the immediate nuclear family available for phenylalanine-tolerance "carrier" studies.

but had never been noticed with the normal brother.

On the left cheek there was a dry eczematous-like rash which had persisted more or less for the past six to eight months despite local ointments. (This disappeared within 10 days after initiation of a low phenylalanine diet and has not reappeared after six months).

A more detailed family history revealed that the mother, age 26 years, although blond and blue-eyed, claimed to be of pure Jewish stock as far back as the family tree could be traced (Fig. 1). She had some of the facial features of this nationality group as did her mother (the patient's maternal grandmother), who also had a rather marked Jewish accent in her speech. The father, age 26 years, had brown eyes and wavy dark brown hair. He claimed to be ⅞ Italian and ⅛ French by descent (Fig. 1). There was no known history of mental retardation, convulsions, or allergies in relatives on either side of the family. However, the maternal grandmother and a paternal aunt had had nervous breakdowns (Fig. 1). Another paternal aunt and one of her five children (by two husbands) were deaf mutes. The father's parents (paternal grandparents of the PKU children) were first cousins (Fig. 1).

COMMENTS

1. A family case history is presented in which two of three children have phenylketonuria (PKU) and between them illustrate many of the frequently encountered features of this disease:

(a) A normal early infancy followed by progressive mental deterioration to levels of moderate to severe mental retardation.
(b) Irritable, withdrawn personality patterns.
(c) Abnormal electroencephalogram.
(d) Smaller than average head circumference.
(e) Relative shortness of stature with increasing years.
(f) Pruitic eczema resistent to standard therapy.
(g) Characteristic musty odor of phenylacetate.
(h) Familial pattern with normal parents and both normal and PKU siblings.

2. This case history clearly demonstrates the advisability of routine testing of all mental defective populations for PKU and of prompt orientation of involved families and family physicians. At least one pamphlet is available to assist in such orientation.[16]
3. All existent and subsequent siblings should be tested.[13,14] Early detection of PKU permits early initiation of a low phenylalanine diet and the opportunity for normal or more nearly normal mental development.[7]
4. This case history demonstrates the usefulness of a simple diaper test[14] (a drop of 10 per cent aqueous ferric chloride solution on a wet diaper to give a green spot which fades within a few minutes) as a screening test for PKU. The diagnosis in the older of the two PKU siblings was delayed by almost two years because of the difficulty in obtaining a urine specimen from this untrained, retarded little girl. By the time the diagnosis finally was made (by a diaper test), another PKU infant had been born into the family and was already 13 months old with a significant degree of irreversible mental retardation.
5. Unrefrigerated, unpreserved specimens of PKU urine will gradually deteriorate largely because of bacterial action. The chance of a specimen having a positive urine test decreases approximately one per cent per hour while sitting at room temperature.[14]
6. Although PKU has been detected in all races and most nationalities throughout the world, it has been particularly rare in people of Negro or Jewish ancestry. The case history presented in this article, we believe, is the second reported instance in the world's medical literature in which one or both parents of PKU children are Jewish. This Jewish mother and her relatives are proud of their nationality background, and they believe they represent a pure Jewish stock. Yet the fair complexion, blond hair, and blue eyes of this young mother do raise the

possibility of some unrecognized or unpublicized outside contamination of the Semetic line somewhere sometime since her ancestors of long ago left Palestine and the near East.

ADDENDUM

Dr. Jon Karlsson has brought our attention to a letter to the editor in the February 11, 1961, issue of *The Lancet*.[17] The authors, Cohen, Bodonyi, and Szeinberg, describe the discovery of five phenylketonuric children in three non-Ashkenazi Jewish families in Israel the past year (one "oriental" and two "Yemenite" families). This led them to examine the urines of defective children in institutions in the country. A preliminary report indicates that an additional five cases of phenylketonuria have been discovered among approximately six hundred patients belonging to the "oriental non-Ashkenazi" Jewish group, a frequency within the 0.5-1.5% range generally reported elsewhere. It is of interest that most of the ten phenylketonuric children (in and out of institutions in Israel) are reported to have dark complexions with dark and even black hair and deep-brown eyes. The diagnoses were verified by serum phenylalanine levels and chromotographic examination of the urines.

Among approximately four hundred patients of Ashkenazi Jewish heritage there were no phenylketonuric patients found. Cohen et al point out that it is the Ashkenazi group who form the majority of Jews in Europe, England, and the United States and this probably accounts for the rarity of phenylketonuria among Jews examined in those countries.

Considering the description of physical characteristics, the countries of residence and the family names of the ancestors on the Jewish side of the family in our report, it is probable that Ashkenazi heritage is mainly involved. We gratefully acknowledge the counciling in this matter from Walter J. Fischel, PhD., Professor of Semetic Languages and Literature, University of California, in Berkeley.

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Hemoglobin C Disease

REPORT OF A CASE IN A 12 YEAR OLD NEGRO

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PERIODIC reports concerning hemoglobin C have appeared in the literature following the discovery of this abnormal hemoglobin by Itano and Neel in 1951.[1] A clinical description has emerged that permits the presumptive diagnosis of homozygous hemoglobin C disease when certain findings are present. These have been summarized by Smith and Krevans,[2] who reviewed the rapidly expanding literature and added 9 cases of their own. This report concerns itself with an additional case of this relatively rare disease and a family study which demonstrates the simple inheritance of the gene that determines the production of hemoglobin C.

CASE REPORT

E. C., a 12-year-old colored boy was admitted to Beth Israel Hospital for the first time on Nov. 2, 1960 because of an enlarged spleen. He had been examined by a physician about a month previously as a routine procedure prior to clearance for dental work at a clinic. Following the examination, the mother was told that the child had an enlarged spleen and follow-up medical care was recommended. The family was then referred by their physician to the clinic at Beth Israel Hospital.

The patient had been in good health, participating in all activities without limitation or restrictions. There had been no weight loss, diarrhea, cough, abdominal or extremity pain, and no evidence of any bleeding tendency. He had the usual childhood illnesses including measles, mumps, and chickenpox and had his tonsils removed at 4 years of age. The family history revealed no evidence of allergies, anemia or blood dyscrasias. The mother's pregnancy was uneventful and he was born by a normal spontaneous delivery.

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He was seen in the pediatric clinic at Beth Israel Hospital on Oct. 26, 1960 and again one week later. On both occasions his spleen was found to be enlarged 4 fingers below the costal margin. The organ was hard and the outline sharp.

A blood count on Oct. 26 revealed Hb 11 grams per cent. The white blood count was 7100 with 50 per cent polymorphonuclear leucocytes and 36 per cent lymphocytes. Many target cells were present. Reticulocytes numbered 1.2 per cent; platelets were 115,000 per cubic millimeter. The hematocrit was 35 per cent. The heterophile antibody titer was 1:14 and the antistreptolysin titer 250 units.

Examination upon admission to the hospital revealed a well nourished, well developed 12-year-old negro youth in no acute distress. The head was normocephalic and the neck was supple with no venous distention. The conjunctivae and sclerae were normal. Fundoscopic examination revealed no pathology. The heart revealed normal rate and rhythm and no murmurs were heard. The abdomen was soft and the liver and kidneys were not palpable. The spleen was enlarged to 4 fingers below the costal margin with a firm and sharp border. Extremities and genitalia were normal.

COURSE IN HOSPITAL

The physical findings remained unchanged during his hospital stay. Urinalysis was negative as was his serology (Kolmer and Wasserman).

A repeat blood count on November 3 revealed 10 grams of hemoglobin and a hematocrit of 30 per cent. White blood count was 8,000 with 67 polymorphonuclear leucocytes and 27 lymphocytes.

Anisocytosis was present and many target cells were seen. Reticulocytes numbered 0.1 per cent and platelets were adequate. The sickle cell prep was negative. Total bilirubin was 1.1 mgms per cent and the direct 0.40 mgms per cent. Heterophile antibody titer was 1.56—ox cells and guinea pig kidney were negative. Tuberculin test was negative.

Electrophoretic studies of the hemoglobin of the parents and siblings were performed and the diagnosis of homozygous hemoglobin C disease was established. The patient was discharged to the clinic for follow-up studies.

FAMILY STUDY

The patient was one of five children. The results of electrophoretic study of the hemoglobin of the parents and siblings is demonstrated in Figure 1. From these findings it is possible to construct a family pedigree showing the inheritance of the gene for the abnormal hemoglobin Figure 2. The result of the hematological examination of the family is presented in Table 1.

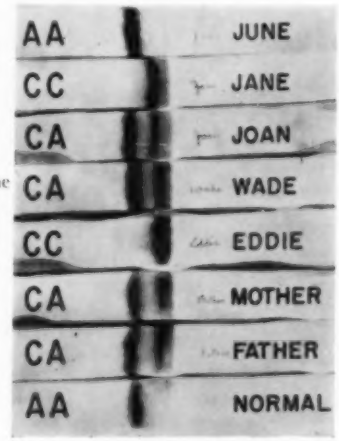

FIGURE 1

Result of electrophoretic study of the Hemoglobin of the parents and siblings.

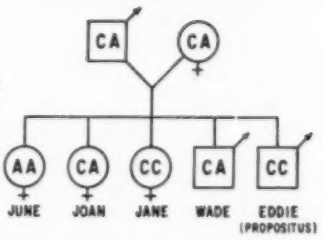

FIGURE 2

Family pedigree showing inheritance of the Gene for the Abnormal Hemoglobin.

A-Normal Adult Hemoglobin
C-Hemoglobin C

DISCUSSION

The preponderance of negroes in the several reported cases is noteworthy. Surveys of colored populations showed an incidence of hemoglobin C of 2 per cent in a random sampling, but no instance was found in the random sampling of a white population.[3] Nevertheless sporadic examples of hemoglobin C in Caucasians have been reported, usually as a single gene in combination with the gene for thalassemia. Diggs reported a case of hemoglobin C disease in

TABLE 1

Result of Hematological Examination of the Parents and Siblings.

	AGE (YEARS)	HGB. GMS	HEM. PER CENT	RBC MILLION	WBC	STAFF PER CENT	POLY. PER CENT	LYMPH. PER CENT	MONO. PER CENT	EOS. PER CENT	BASO. PER CENT	RETIC. PER CENT	TARGET CELLS PER CENT	PLATELETS	SICKLE CELLS	SPLEEN	TOTAL BILIRUBIN MGMS PER CENT	DIRECT BILIRUBIN MGMS PER CENT
Father	36	12.5	40	4.35	9900		57	40	2		1	0.1	4	220000	neg	neg	0.20	0.04
Mother	34	11.5	38	4.12	6600		62	33	3	2		0.2	6	180000	neg	neg	0.40	0.08
Eddie (propositus)	12	10.1	30	3.71	8000		67	27	4	2		0.1	25	190000	neg	4f.	1.11	0.40
June	11	10.5	38	4.28	9100		50	43	5	2		none	1	180000	neg	neg	1.19	0.04
Joan	9	11.5	37	3.60	11700		34	55	8	3		0.2	17	98000	neg	neg	0.40	0.04
Wade	6	10.5	30	3.42	11900		49	36	7	8		0.1	5	116000	neg	neg	0.60	0.20
Jane	3	9.0	31	2.85	11200	1	46	42	5	6		0.2	26	310000	neg	neg	0.80	0.20

a white male of Italian descent in 1954.[4] Huisman described the occurrence of this abnormality in a family of Dutch extraction although here the possibility of negro ancestry was considered.[5] Homozygous C disease has been reported in a white family in Capetown, South Africa.[6] Galbraith, in 1960 reported the first sample of hemoglobin C disease to be encountered in an Anglo-Saxon family.[7]

The characteristic finding of splenomegaly in a relatively asymptomatic negro with signs of a mild hemolytic process should arouse the suspicions of the clinician. The presence of a slight anemia with large numbers of target cells in the peripheral blood smear is usual. The hemolytic process can be established by the finding of a moderate reticulocytosis, an increased indirect bilirubinemia and an increased urobilinuria. The absence of severe crises, skeletal abnormalities and general symptoms differentiates this mild disease from the more severe sickle cell disease. The final definitive proof is the electrophoretic pattern which demonstrates the characteristic slow mobility of hemoglobin C when compared to hemoglobin S and A.

The genetic aspects of the inheritance of C hemoglobin are interesting in that it is considered an autosomal dominant character with incomplete expression. In combination with other hemoglobin abnormalities with which an allelic relationship exists, a summation effect is produced resulting in clinical disease.[8] The combination of sickle cell—hemoglobin C disease is recognized and produces a more profound disease than does homozygous C disease itself.[9] The

hemoglobin C-thalassemia combination similarly produces a disease of greater clinical significance.[10] The mathematical possibilities of a homozygous form of hemoglobin C occurring where the heterozygous form exists in only 2 per cent of the colored population is .04 per cent or 1 in 2500 of random people. At such low levels of frequency, consanguinity is a frequent finding, and should be asked for in the history.

SUMMARY

1. The finding of a relatively asymptomatic splenomegaly with large numbers of target cells in a colored person should arouse the suspicion of hemoglobin C disease.

2. The characteristic pattern on paper electrophoresis establishes the diagnosis and differentiates this disease from the other more serious hemoglobinopathies.

3. Family studies can establish the genetic nature of the abnormality and lead to a better understanding of its transmission.

We are grateful to Dr. Leon N. Sussman of the Department of Hematology and to Dr. Ella Fishberg of the Department of Biochemistry for their aid and advice.

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Treatment of Catarrhal Symptoms in Measles . . .

EVALUATION OF A NON-NARCOTIC THERAPEUTIC AGENT

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IN UNCOMPLICATED cases of measles, the catarrhal symptoms may cause not only extreme distress to the patient but confront the pediatrician with a most difficult problem of satisfactory control. The coryza, conjunctivitis and frequent sore throat, and the accompanying malaise, headache and fever constitute major sypmtomatic complaints. A particularly aggravating complaint is the severe cough so characteristic of measles. Deep-seated, racking and exhausting, its deleterious effects on the patient far exceed any function it may serve in the clearing of secretions. It adds greatly to the discomfort of the patient and actually delays convalescence by interfering with sleep and rest.

The cough reflex serves as a means of expelling foreign bodies and excess secretions from the respiratory tree in disease conditions where the mucous membranes of the tract are directly involved, but frequently the degree of coughing is out of proportion to any protective function the cough might serve. It is instigated by an inflammatory reaction which causes constant abnormal stimulation of efferent pathways of the cough reflex having their receptors in the edematous, erythematous, mucous membrane. This cough is not only annoying and troublesome, but it may spread infections to previously uninvolved portions of the respiratory tract, and when severe, may cause physical damage such as rupture of the blood vessels, alveoli or muscle and fascial layers of chest and abdomen.

Cough preparations are conventionally used in measles in deference to the demands of parents and patients, as well as for therapeutic effect, but the desired results are usually minimal. Large doses of narcotic cough mixtures promote intestinal stasis and central nervous system depression, both already prominent problems characteristic of the disease entity itself.

During the autumn of 1959 and the winter and spring of 1960, a particularly heavy outbreak of measles occurred in this locality. At that time, there was made available to us a non-narcotic preparation which appeared particularly well suited for treatment of the catarrhal symptoms of the disease.* It contained choline salicylate,

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an effective analgesic and antipyretic that acts more rapidly than aspirin and produces blood level peaks of salicylate within 10-12 minutes after administration.[1,2] Moreover, it has been reported to induce much less gastrointestinal distress than equivalent dosages of aspirin in a significant percentage of patients.[2,3] This was especially important in measles, where a hemorrhagic gastritis may be encountered. Secondly, it contained L-phenylephrine hydrochloride, a vasoconstrictor, the most effective and least toxic of the sympathomimetic amines in this action[4] and chlorpheniramine maleate, one of the most potent antihistamines.[5]

The latter two agents appeared well adapted to provide symptomatic relief for the coryza accompanying measles. In addition, although the rationale for their use in this respect may not be clear, antihistamines are finding increasing acceptance as components of cough medications and have been reported as contributing to the effectiveness of the latter. Since salicylates have also been reported as providing effective topical analgesia to the pharynx, choline salicylate might be expected to afford symptomatic relief of any sore throat. Further, by such action it might conceivably block any afferent impulse to the reflex cough arc originating from the irritated and inflamed pharyngeal mucosa.

All of these drugs have wide margins of safety and little or no side effects. We took the opportunity to try the effectiveness of this combination in treatment of the catarrhal symptoms in a number of acutely ill children with measles, using for comparison a simple syrup which contains a widely used narcotic and allegedly very effective cough depressant.

METHODS

Forty-four children were studied, ranging in age from 1½ to 16 years and acutely ill with measles either in the pre-eruptive phase when Koplik spots could be found in large numbers, or in the early stages of eruption. All the patients were treated at home and examined twice over at least a five-day period, with daily telephone contact to the parents.

Two mixtures were used: The test mixture—A—contained:

Choline salicylate—870 mgms. (equivalent in salicylate content to 10 grains of aspirin)
Chlorpheniramine maleate—2 mgms.
L-phenylephrine hydrochloride—5 mgms.

[4] Kindly supplied by the Medical Department of The Purdue Frederick Company, New York, containing per teaspoonful, 870.0 mgm. Choline Salicylate, 5.0 mgm. L-phenylephrine hydrochloride and 2.0 mgm. chlorpheniramine maleate.

The dosages used were ¼ teaspoonful for ages 2 to 6 years, ½ teaspoonful for ages 6 to 12 years and 1 teaspoonful for ages 12 years and over. The medication was prescribed for administration every six hours and no other medication was given.

The second preparation (mixture B) was a syrup of dihydrocodeinone bitartrate (5 mgms. to the teaspoonful), given in the same dosage schedule. The preparations were given to alternate patients, as each case of measles presented itself.

At the end of the study, the two groups were evaluated by both objective and subjective criteria and the results tabulated in the following categories:

1. General Condition—An impression obtained through questioning of the patient, by observation on at least two occasions by the clinician and by a daily report from the parent. Improvement was indicated by decrease in the severity of coryza, conjunctivitis, sore throat, malaise, headache and fever.
2. Severity of Cough—An impression gained by subjective evaluation through both clinical and parental observation.
3. "Cough Count"—Over a two-minute period, a count of the number of coughs was taken by the examining physician. With the onset of a spasm of coughing, counting was begun for a two-minute period. This procedure was repeated three times and the average of the three periods was designated as the "average cough count." These counts were made at least 24 hours after the institution of therapy.
4. Cough Complications—The conditions considered as cough complications were:
   a) Petechial hemorrhages around face and head.
   b) Blood in sputum.
   c) Vomiting occurring after coughing spasms.
   d) Pain in chest or abdomen.
   e) A miscellaneous group of all other complications occurring in this study (subconjunctival hemorrhages, hernias, etc.)

RESULTS

After a minimum of five days of therapy with the choline salicylate preparation, 21 of 22 patients demonstrated some degree of improvement in their catarrhal symptoms and their general condition. In six patients, the degree of improvement was excellent; in nine, moderate; only minimal improvement was noted in six patients. Of the twenty-two who were given the control prepara-

tion, 11 children showed minimal improvement, and 11 others none at all, as is shown in Table I.

As to improvement in the severity of cough, 16 patients coughed appreciably less severely during treatment with the choline salicylate-containing preparation; whereas, 13 patients showed only minimal improvement in cough severity on the control preparation, a narcotic cough depressant, and nine none at all. Table II summarizes the comparative evaluation of the cough count averages and observed complications.

DISCUSSION

There are many difficulties in attempting to make a study of this type conform to the desirable rigid criteria of standardization, selection and control. Yet, there is considerable information that can be gained by investigations of this nature in specific situations. In this study, the evaluation of a therapeutic modality, indeed, if only for the symptomatic treatment at home of mild or moderately severe type of measles during a brief period of observation, nevertheless permits a statement of clinical impression, if not an exact controlled comparison. Our two study groups, selected on an alternate basis, differed slightly in composition as far as age is concerned, the group treated with mixture A being of a slightly older average age. Also, we are mindful that the disease itself varies tremendously among individuals and that this variation can only be diminished in its significance in a controlled study by increasing the number of cases in the study many fold.

However, within the limitations of this study, certain conclusions may be drawn in a general manner: Firstly, almost all of the cases felt varying degrees of improvement in their catarrhal sypmtoms and their general condition when taking mixture A (21 out of 22 cases), as compared with mixture B (11 out of 22 cases). Secondly, most of the children felt that they coughed less severely when they took mixture A (16 out of 22 with significantly decreased coughing, as compared with 13 out of 22 with only insignificant reduction in coughing when taking mixture B).

The average cough count (as defined above) was 62 in the group treated with mixture A and 74 in the group treated with dihydrocodeinone bitartrate. A total of 11 complications of cough occurred in the group treated with the choline salicylate-containing medication and 24 were noted in the other group.

TABLE I

DEGREE OF IMPROVEMENT IN CATARRHAL SYMPTOMS AND SYSTEMIC COMPLAINTS AND SEVERITY OF COUGH IN 44 CHILDREN ACUTELY ILL WITH MEASLES DURING TREATMENT WITH TWO MEDICATIONS

	Catarrhal Symptoms and Systemic Complaints			
	Degree of Improvement			
MEDICATION	Excellent	Significant	Minimal	None
Mixture A (See Text)	6	9	6	1
Mixture B (dihydrocodeinone bitartrate)	0	0	11	11

	Severity of Cough			
	Degree of Improvement			
MEDICATION	Excellent	Significant	Minimal	None
Mixture A (See Text)	0	11	5	6
Mixture B (dihydrocodeinone bitartrate)	0	0	13	9

TABLE II

COMPARISON OF RESULTS IN COUGH COUNT AVERAGES AND OBSERVED COMPLICATIONS DURING ADMINISTRATION OF TWO MEDICATIONS TO 44 PATIENTS ACUTELY ILL WITH MEASLES

MEDICATION	Cough Count Averages	Observed Complications*
Mixture A (See Text)	62	A— 2 B— 4 C— 7 D— 1 E— 0
Mixture B (dihydrocodeinone bitartrate)	74	A— 7 B— 4 C—10 D— 2 E— 1

* A—Petechiae of face and neck.
B—Blood in sputum.
C—Vomiting after cough spasms.
D—Pain in chest and abdomen.
E—Miscellaneous other complications.

We may say that the combination of choline salicylate, chlorpheniramine maleate and L-phenylephrine hydrochloride proved at least as, if not more, effective than a standard cough mixture in controlling the cough of measles, and was considerably better than this widely used narcotic medication in providing symptomatic relief.

SUMMARY AND CONCLUSIONS

1. Two types of medications were compared in the treatment of the non-exanthematous complaints of a group of 44 children acutely ill with measles. Attention was paid to the so-called catarrhal symptoms of coryza, conjunctivitis, sore throat and the accompanying malaise, headache and fever and in particular, to the characteristic severe cough. The first non-narcotic medication contained choline salicylate, chlorpheniramine maleate and L-phenylephrine hydrochloride. The second medication contained the narcotic, dihydrocodeinone bitartrate, as an antitussive and analgesic agent.

2. The choline salicylate-containing preparation was found to be much more effective in relieving symptoms of coryza, conjunctivitis, sore throat, headache and malaise, and in accelerating defervescence. Coughing was significantly decreased in 11 of 22 patients treated with it, with minimal decrease in five others. A significant degree of decreased coughing was not observed in any of the 22 patients treated with dihydrocodeinone bitartrate, but a minimal decrease occurred in 13 of these, as evaluated by a special technique described in this report. The average "cough count" (the number of coughs in spasms of two minutes' duration) was 62 in the group treated with the choline salicylate-containing medication and 74 in the group treated with the dihydrocodeinone bitartrate. A total of 11 complications of cough, such as hemorrhage, vomiting, etc., occurred in the first group and 24 in the second group.

3. No cases of constipation nor of clouding of the sensorium which could be attributed to drug therapy occurred in the group treated with the combination of choline salicylate, chlorpheniramine maleate and L-phenylephrine hydrochloride.

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Activities of The Poison Control Center . . .

PHOSPHORUS POISONING INCLUDING TWO FATAL CASE REPORTS

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WE ARE indebted to Dr. Barbara Parker of the Psychiatric Medical Division of Bellevue Hospital for the following case reports:

CASE 1

The patient, a 39-year old Puerto Rican male, was admitted to Ward A1 on July 8, 1961 approximately one hour after ingesting a quantity of J-O Paste somewhere between two and three teaspoons and one-half can. Patient at that time complained of sharp abdominal pain immediately after ingestion. He had no history of previous suicide attempts. Significant past history includes malaria in 1940 and large alcoholic ingestion.

Physical Examination: A well-developed, well-nourished Puerto Rican male in no acute distress. Pulse 88; respiration 16 and irregular; blood pressure 130/80, left arm recumbent. Head: traumatic, normocephalic. Eyes: pupils equal, react to light and accommodation. Nose: trauma to the nostril secondary to passing of Levine tube. Mouth: lips and tongue normal without burns or discoloration. Teeth: in good repair. Posterior: pharynx unremarkable. Ears: normal. Neck: supple. Veins: flat. Chest: clear. Heart: regular sinus rhythm without murmurs or thrills.

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Abdomen: soft, non-tender. Organs: not palpable. Old appendectomy scar in right lower quadrant. Genitalia: uncircumcised, testes normal, without masses. Rectal: normal prostate, without nodules, without masses. Neurological: within normal limits. Skin: without icterus or spider angiomata.

Laboratory Findings: Initial urine: yellow, clear. Specific gravity 1.008 without glucose, acetone, bile or protein. Urobilinogen present in one to four dilution, without white cells, red cells or casts. During the hospitalization, specific gravity was 1.020 and then became fixed at 1.010. Urobilinogen increased to 1-20 dilution and bile became present in the urine. Protein increased to one-plus. White cells appeared in quantities of 8-10 per high power field and terminally red cells were present, 10-14 per high power field. There were never any casts present. Urine sodium was traced in the 24-hour specimen. Potassium: 13 mEq/ per liter and Cl 35 milequivalents per liter with a total 24-hour output of 660 ml. Initial Hemoglobin: 11.3 grams; hematocrit 39%; erythrocyte sedimentation rate 2; white blood count 5,570, differential normal. These levels were stable. The prothrombin time was one minute and 7 seconds for the patient, over a control of 15 seconds. Initial BUN: 33, rising to 47, 67, and 76. Creatinine: 6.6. Blood Sugar: 178 and 63, both without IV's running. CO 2: Initially 26, then 21, then 12. Initial Sodium: 157, 132, 130, 125, 116, 106. Potassium: Initially 3.7, 3.5, 4.2, 4.3, 6.0, 7.5. Serum Phosphatase: 3.5 and 4.9. Alkaline Phosphatase; 6.0, 6.1. Thymol Turbidity: 4.0, 3.0. Cephalin Flocculation 0 and 3. Albumin Globulin Ratio: 3.0/3.5 and 4.0/3.2. Cholesterol/Esters: 113/49, 108/61. Bilirubin: 1.6, 5.4, 11.8. Transaminase: 51/64, 360/250, 1,980/1.510, 1,635/1,210. Uric Acid: 18.2. Serologic Test: negative. Blood pH: Terminally 7.39. Initial Stool Guaiac: negative, later became positive. Gastric Aspirates: Guaiac positive.

Course: While in the General Hospital, patient was treated as a presumptive Drano ingestion and was lavaged with 500 cc of 1% acetic acid. It then appeared that the patient had not taken Drano, but J-O Rat Poison containing phosphorus, and then patient was lavaged with a 1-1,000 dilution of potassium permanganate with a total of 3 liters. The patient was then seen by an ear, nose and throat consultant, who treated him for a caustic ingestion. Management included a Levine tube, nothing by mouth and steroids, using Metacortin, 80/mg. the first day, 60 mg. the

second day, 40 mg. the third day and 20 mg. thereafter. Plans for esophagoscopy were made to follow later. The patient was transferred to the Psychiatric Hospital on the second hospital day and the regimen outlined by the ear, nose and throat consultant was followed. The patient appeared relatively well.

On the third hospital day, the patient still appeared relatively well but was becoming weaker. It was then noted that his transaminase levels were rising and protein was appearing in the urine but no other changes were noted. On the fourth hospital day, the patient became icteric and the icterus deepened rapidly over a period of eight hours. His bilirubin was noted to have risen from an initial 1.6 to 11.8 and transaminase from high normal levels to astronomical levels. Also on the fourth hospital day, the patient became much weaker, developed hiccups and episodes of vomiting and the urine output began to diminish to 300 cc. On the seventh hospital day, weakness increased and the patient began to ooze blood from the nose and mouth and to drain Guaiac positive material via Levine tube; vomiting persisted. Urine output decreased to 275 cc and the patient was treated as an acute renal failure. On the eighth hospital day, the patient became far weaker and restless and his blood pressure began to fall. The electrocardiogram at this time showed a change from the previous one with markedly increased height of the T waves. Serum potassium at this time was 7.5 mEq/ liter. It was then noted that the patient's blood did not clot, while previously it had. Later in the day, the patient began Cheyne-Stokes respiration and then expired. The final diagnosis was acute phosphorus poisoning. The autopsy was done by a Medical Examiner and we are grateful to Dr. Milton Helpern, the Chief Medical Examiner for the following report:

Chest: Each pleural cavity contains approximately 50 cc of serous sanguinous fluid. The pleural surfaces are smooth and glistening. There is an extensive hemorrhage in the mediastinal soft tissue and the pericardium, both the visceral and parietal. The pericardial cavity contains approximately 30 cc of yellow fluid and the surfaces are smooth and glistening.

Heart: The heart weighs 280 gms. There are numerous petechial hemorrhages in the visceral pericardium. The myocardium is light red-brown. The endocardium is smooth and glistening. The valves are thin and pliable and translucent. The coronary arteries display no atherosclerosis or occlusions. The great vessels and aorta pursue a normal course and present the usual number

of branches. Displays minimal focal lipid streaking of the abdominal portion.

Lungs: The combined weight of the lungs is 1280 gms. There is some diminution and crepitance in the lower lobes. The cut section reveals large areas of streaky hemorrhage. The pulmonary arteries display no atherosclerosis of thrombo emboli. The bronchi are moderately reddened and contain a moderate amount of gray-white mucoid material.

Liver: Weighs 1250 gms. Capsular surface is yellow and smooth. Cut section reveals a light yellow-brown color which is a moderately greasy consistency. The yellow is distributed irregularly, in some areas it is more heavily concentrated and the individual lobular pattern cannot be made out. Elsewhere, there are fine focal lobules, which are yellow and are separated by small depressions.

Spleen: Weighs 70 gms. The external surfaces are gray-purple. Cut section reveals a soft red-brown parenchyma with focal areas of hemorrhage.

Adrenals: Are natural. Yellow cortex is noted.

Kidneys: Are alike and have a combined weight of 480 gms. The capsule strips with ease revealing a smooth capsular surface. The cut section the parenchyma bulges. There is moderately good cortical medullary differentiation with a slight suggestion of greasy consistency. The pyramids, pelves and ureters are natural.

Urinary Bladder: There is a focal area of hemorrhage at the dome.

Gastrointestinal Tract: The esophagus is glazed; areas of hemorrhage at its lower portion. The gastric mucosa contains numerous focal 1 cm. areas of ulceration containing dark black-changed blood at its base. The stomach contains approximately 400 cc of inky liquid with fine black particles. The remainder of the small intestine, large intestine, appendix and rectum contain no evidence of bleeding. The terminal portion of the colon and rectum contains semisolid green-brown fecal material.

Neck Organs: The intense hemorrhage in the mediastinal structures extend up into the soft tissues of the neck. The esophagus is natural in this area. The trachea and larynx and thyroid are likewise natural. The cervical blood vessels are free of atherosclerosis or occlusions.

Section of Head: The removed brain weighs 1260 gms. Numerous cut sections display no lesions. The blood vessels at the

base of the brain display no atherosclerosis or occlusions. There are no fractures of the skull.

Osseous System: This is intact and natural.

Anatomical Diagnosis: Fatty degeneration and necrosis of liver. Acute nephrosis. Intense hemorrhages in mediastinal soft tissue, lungs and spleen. Specimens saved for toxicological examination; kidney and liver for phosphores. The results have not yet been obtained.

CASE 2

The second fatality involved an 18-year-old white female who ingested one-half can of J-O Roach Paste with suicidal intent. On admission to the hospital patient stated she has troubles and is determined to solve them. Soon after ingestion, patient vomited and had abdominal pain and nausea. Several hours later, patient was admitted to a hospital. The stomach was lavaged with hydrogen peroxide; she was also given mineral oil and Demerol. She was put on a high protein, high carbohydrate and low fat diet. The blood transaminase was over 260 units. Hematocrit 23%. The prothrombin time over 60 seconds over a control of 15 seconds. The leucocyte count was 16,000 and the hemoglobin 13.1 grams. The platelet count was 90,000, CO_2 8 Vol.%.

The cephalin flocculation test was 4+ and the thymol turbidity 1.4. The urine contained trace amounts of elemental phosphorus and a distillation of 25 grams of muscle-tissue showed presence of elemental phosphorus.

Cause of Death: Fatty degeneration and necrosis of liver. Acute nephrosis. History of phosphorus ingestion. Suicidal. Phosphorus is available in two forms. "Red" phosphorus which is insoluble, non-volatile and non-toxic and "yellow" or "white" phosphorus, which is readily soluble in oils, absorbable and highly toxic. It has a characteristic odor of garlic. Yellow phosphorus is widely used in the manufacture of pesticides and fertilizers. Acute phosphorus poisoning was very frequent several decades ago, when it was also used in the manufacture of matches, medicinal preparations and fireworks. Fortunately, its use in matches and fireworks has been eliminated through wise legislation. It is hoped that with the availability of safer and equally effective chemicals, its use in the manufacture of rodenticides and insecticides will also be eliminated.

Toxic Effects: Phosphorus causes cellular damage and disturb-

ances of protein, fat and carbohydrate metabolism. It inhibits the deposition of glycogen in the liver and increases the storage of fat. It is slowly absorbed from the gastro-intestinal tract and respiratory mucosae. Its toxicity is increased, however, when it is in a solution, in the form of an emulsion. The inhalation of phosphorus may cause acute poisoning similar to that following ingestion. Skin contact may cause severe second or third-degree burns which are frequently accompanied by sepsis. The lethal dose for an adult is estimated between 60 miligrams and 1 grain, and the fatal dose for a child is much lower. There is marked individual variation to susceptibility. A recovery has been reported from the ingestion of 825 mg. and a fatality in a two-year old child from the ingestion of as little as 3 mg. (One mg. per kilo of body weight is considered a lethal dose.)

The symptoms of acute phosphorus poisoning are of local and systemic origin, for phosphorus is both a local irritant to the gastrointestinal tract and also produces systemic manifestations causing injury to the cells of the liver, kidney, brain, muscle, bones, as well as to the cardiovascular system. The course of acute poisoning may be manifested in three stages. In the first stage gastro-intestinal symptoms predominate, such as abdominal pain, burning in the throat, nausea and vomiting. This may occur immediately after ingestion or several hours later, and may last from a few hours to several days. The vomitus has characteristic garlicky odor and is luminous in the dark. It may also contain blood. In severe phosphorus poisoning patient may become prostrated within several hours following ingestion develop a bloody diarrhea, become lethargic, develop shock, collapse, and may die within 10 hours following ingestion. Early shock is a poor prognostic sign. After the first stage, the second stage is ushered in. This is a relatively "symptom free" period of several days' duration. Patient appears temporarily improved with an abatement of the gastro-intestinal symptoms manifested in the first stage. This latent period of several days' duration, however, is soon followed by the third or the "systemic" stage. The gastro-intestinal symptoms which appeared in the first stage and were chiefly due to gastric irritation, now become very severe and result from systemic toxicity. The vomiting is associated with a bloody diarrhea. The mucous membranes of the mouth and pharynx become very pale and ecchymotic. Marked injury occurs to the liver, kidney, heart and brain. The liver becomes enlarged and tender and patient

becomes jaundiced. Due to kidney damage patient may develop hematuria oliguria, anuria, an azotemia and perhaps a uremia. Due to injury of the cardiovascular system, electrocardiographic changes occur, and patient may go into circulatory collapse. The pulse becomes thready, the blood pressure falls and the respirations become shallow and rapid. Because of brain damage the patient becomes confused, disoriented, lethargic, comatose, delirious and may develop convulsions before death. The blood picture is variable.

Acute phosphorus poisoning offers a poor prognosis. The case fatality rate is over 50%. Death usually occurs within 8 days but it may be delayed for several weeks. Early liver enlargement and jaundice are indications of a poor prognosis.

Dr. Parker relates some interesting clinical data with statistics as follows: In our series of 112 patients admitted with phosphorus ingestion, thirty-four have died. Of the twenty-eight who developed early jaundice, thirteen have died and 15 have lived. Thus the case fatality rate in persons who developed early jaundice was significantly higher than in the overall groups. The treatment is chiefly directed toward eliminating the toxic substance before it becomes absorbed by means of induced vomiting and gastric lavage with potassium permanganate and/or with copious amounts of water. Hydrogen peroxide in a concentration of 2% or a 0.2% solution of copper sulfate may also be used to delay absorption due to a coating of the phosphorus particles with an insoluble copper phosphide. In addition to lavage the treatment in the absence of a specific antidote is entirely symptomatic and supportive. It is also advisable to treat any case as a potential acute hepatitis.

Since the beginning of 1961, 32 cases of phosphorus *poisoning* ingestions have been reported to the New York City Poison Control Center with two fatalities. Of these, 17 were males and 15 were females. (No sex variation.) Twenty-four of the 32 individuals who ingested phosphorus were children 3 years and *under* who ingested phosphorus accidentally. The usual mode of occurrence is due to the patient's finding a sliced potato on which J-O Paste is smeared and left on the kitchen floor. The unsuspecting child finds it, licks the phosphorus off the potato, and ingests it. Physicians should discourage families under their supervision from using phosphorus rodenticides. The anticoagulants such as Warfarin are much safer and equally effective agents.

125 *Worth Street, New York* 13

(This is the twelfth of a series of papers by Dr. Jacobziner)

Pediatric Conference . . .

CASE PRESENTATIONS FROM PEDIATRIC DEPARTMENT,
MISERICORDIA HOSPITAL, BRONX, NEW YORK,
VINCENT P. CASEY, M.D., *Director*

Cytomegalic Inclusion . . . Rheumatic Fever—Part II*
PRESENTED BEFORE BRONX PEDIATRIC SOCIETY AT
MORRISANIA HOSPITAL AUDITORIUM—MARCH 8, 1961

Discussors: C. JOSEPH DELANEY, M.D., *Attending Surgeon*
JAMES T. DANIELS, M.D., *Chief Neuro-Surgeon*
HARRY BUCALO, M.D., *Director of Pathology*
CESARE E. CUCCI, M.D., *Asst. Att. Pediatric Cardiologist . . .*
All at Misericordia Hospital

THE third case will be one of cytomegalic inclusion disease. It will be presented by Dr. Wacthel.

DR. WACTHEL: The patient was a 10-day old white female infant born at Misericordia Hospital after 43 weeks of gestation. The medical histories of both parents were entirely non-contributory, and the pregnancy was uneventful. No previous pregnancies. Approximately 17 days prior to delivery, x-ray pelvimetry revealed an adequate pelvic outlet, a relatively small fetus, and a suggestion of polyphydramnios. About 10 days prior to delivery, the fetal membranes ruptured spontaneously and amniotic fluid continued to escape until the date of delivery. During this period the mother received combiotic daily. She never manifested fever and there were no signs of distress or illness. The day following spontanous rupture of the membranes, an attempt to induce labor was made but without success. Another attempt was made on the second post-rupture day with quinine, again without success. Delivery was performed by an elective low-forceps procedure about 8 days later. During the delivery the placenta separated and the umbilical cord, which was described as having been short ruptured but did not bleed excessively. The amniotic fluid was stained with meconium. The mother's post-partum course was entirely uneventful. The pertinent laboratory data indicated blood group O, type Rh positive. A serological test for syphilis was negative. The infant weighed 5 pounds, 10 ounces. Immediately upon delivery no remarkable features were observed. Approximately one hour after birth, however, slight jaundice was noted and numerous skin petechiae were seen. The infant, however, was found to be active

* The reports here presented are two of four discussed at the Meeting recorded. The September issue presented the first and second cases: Bliary Atresia and Recurrent Craniopharyngioma.

with a strong cry and in no apparent distress. The moro reflex was present and normal. Both anterior and posterior fontanels were flat. The suture lines were normal and the head was of the usual size and shape. Examination of the eyes, ears, nose and throat failed to reveal any abnormalities with the exception of a slight yellow tint of the sclerae and a small bilateral sub-conjunctival hemorrhage. The lungs were clear. Heart revealed normal sinus tachycardia and no murmurs. The umbilical stump was not unusual. The liver was 2 centimeters below the right costal margin and was described as firm. The spleen also apparently was firm and could be palpated 2 centimeters below the left costal margin. The external genitalia were normal. There were no abnormalities in the extremities.

The laboratory data: Hemoglobin 16.6 grams, hematocrit 47%, white count 22,000, 62 polys, 24 lymphs, 23 bands, 32 juveniles, and 4 monocytes, 5 eosinophils. 83 nucleated RBC's per 150 cells (R red cells); platelet count 54,000. The infant's blood group was O, Rh negative. Direct and indirect Coomb's tests were negative. Bleeding time was greater than 20 minutes and clotting time was 11 minutes and 54 seconds. A Fibrindex test failed to clot after 5 minutes.

The urine was found to be dark amber and alkaline. Albumin was 2+ 4-6 white blood cells as well as 2-3 red blood cells were found per high power field. Numerous epithelial cells and occasional hyaline casts were also seen. The urine revealed 4+ bile reaction. Urinary urobilinogen was negative. Stool guaiac was 3+. Ceph. flocc. 4+. Examination of bone marrow was non-contributory. Skull x-ray failed to show any evidence of calcification. During the next 10-day period, the infant's liver and spleen progressively enlarged and jaundice likewise progressively deepened. No new petechiae appeared after the 2nd day of birth. The infant was given vitamin K, vitamin C, penicillin and gamma globulin. On the 4th day of life, 75 cc of whole blood was given. On the 10th day the infant began to bleed moderately from the vagina and had several episodes of regurgitation of reddish brown fluid, following which the infant expired.

DR. FRIED: The case will be discussed by Dr. Bucalo, who is Director of Pathology at Misericordia Hospital.

DR. BUCALO: I remember this baby well. Dr. Castrovinci, who was the Director of Pediatrics at Misericordia at the time, was

good enough to ask my opinion because this baby did stump us for a while clinically, and one of the things that occurred to me, and I was interested to hear Dr. Delaney mention this, was the possibility of so-called giant cell hepatitis in this child; it wasn't until several days later that Dr. Cucci came up with the correct diagnosis of cytomegalic inclusion disease. Of course, we had a bit of a merry-go-round for the first four or five days. The usual disease entities which have to be taken into consideration with this kind of clinical problem were sepsis and erythroblastosis, which this resembles very closely; toxoplasmosts was considered, and we found no evidence of intracranial calcification in this baby.

As I remember, Dr. Carl Smith the pediatric hematologist at New York Hospital was called into consultation. He felt that leukemia should be ruled out, which was done following bone marrow examination. This didn't leave us with much else and we proceeded to do cytologic studies on this child's urine. We were never able to demonstrate inclusion bodies in the urinary sediment of this baby which is one of the easiest, quickest and best ways of making this diagnosis. I am given to understand that inclusion bodies can be found in some of the cells obtained in the spinal fluid as well. As I recall, this was not attempted in this baby. The Mother's serum, I might add, was studied for evidence of toxoplasmosis. The specimen was sent to the U. S. Public Health Laboratory in Chandley, Georgia, where the dye study and the compliment fixation studies were done, each of which gave no evidence of toxoplasma infection. I think I should state at this point that the lack of intracranial calcification in this baby was helpful in a negative sense, but if it had occurred, it would mean not only toxoplasmosis, because calcification can and does occur with cytomegalic inclusion disease.

Now at autopsy, the striking feature in this child was the extensive bile staining of almost all the organs and bodily tissues. We examined the liver and biliary tree very closely during the dissection and found no evidence of any developmental anomaly in that area whatsoever. Aside from a deep greenish discoloration, the liver was surprisingly healthy-looking. The kidneys looked perfectly normal with the possible exception of a mild hydronephrosis. The lungs showed evidence of nodular consolidation. There were no developmental anomalies of the cardiovascular system or of the gastro-intestinal tract aside from the biliary tree which has already been mentioned; in the light of these apparently normal gross

findings, the microscopic changes are really quite striking. I should say here we did not have an opportunity to examine either the placenta, or the umbilical cord in this baby.

This slide is a low-power view of the lung and shows the hyperdistended alveolar ducts and alveolar spaces in contrast to the areas of consolidation which were lobular and rather nodular in character.

This one is a higher magnification of one of the consolidated areas. It shows a moderate degree of red cells, within the alveolar spaces, small clusters of macrophages, with foamy cytoplasms which suggest ingestion of formula—almost a normal occurrence in babies of this age. One of the striking things here is the apparent total absence of evidence of inclusion bodies in the lung. The clinical picture this baby presented is quite characteristic of the fulminant and almost universally fatal type of inclusion body disease as occurs in a newborn, and it is common under those circumstances—that is, the circumstances which this child presented so classically—to find evidence of generalized inclusion body disease in almost every organ in the body. They were totally lacking in the lung.

This slide shows that in other areas of the lung a marked amount of edema fluid was found in the alveolar spaces and interestingly enough, there is a suggestion of what one might loosely and nonspecifically refer to as a hyaline membrane formation against the walls of these alveolar spaces. I think it simply represents here a condensation of some of the edema fluid as a result of the increased inspiratory efforts. The liver, of course, showed some fascinating changes. One of the striking things about it was the occurrence of these peculiar giant cell type transformations of the parenchymal cells proper.

Earlier this evening Dr. Delaney mentioned the almost hopeless attempts at trying to differentiate obstructive jaundice from so-called non-obstructive jaundice in the neonate. The point is quite well taken and I'm very grateful that he did not subject me to this trial, because the picture one sees or can see in biliary atresia in a neonate, is almost identical with what we see here. These giant cells do occur; they are plugs of bile. The Kupffer cells are heavily laden with bile and there is a suggestion of proliferation of young biliary radicals. This lesion used to be considered a form of hepatitis. It was believed to be of viral etiology and this point is now seriously questioned; one of the other explanations offered

is an anatomical one, to the extent that the biliary radicals are believed to have escaped from the ordinary control mechanisms, which result in proper linkage with the liver cell plates, so that there is an interference of normal bile flow with an accumulation of bile in the liver and spillage.

This slide is simply a higher magnification to bring out in a little more detail some of the rather striking giant cell forms that one sees—the plugged bile in some of the smaller canaliculi.

This slide shows one of the other striking changes in the liver was the foci of extra-medullary hematopoesis which were scattered throughout. They were very pronounced and they were entirely consonant with this type of change, as one sees it, in erythroblastosis.

This slide shows a section of the spleen, and once again, some rather striking ectopic hematopoesis in the splenic sinusoids, again a picture that is far beyond what one sees normally in a newborn and is entirely in keeping with the changes seen in erythroblastosis.

This shows a section of pancreas, and once again large islands of ectopic blood-forming cells are found scattered throughout.

And this one, a section of adrenal, once again showing islands of extra-medullary hematopoesis. The one striking thing in all these sections and all these organs, was the absence of inclusion bodies in the cell nuclei.

Now this one is a section of the infant's kidney, and here at last, we have the pathognomonic change which gives us our diagnosis and diagnostic terminology. These are renal tubules. This is one; this is another (indicating). This is a well formed renal glomerulus. The striking thing here, of course, is the large ovid basophilic staining inclusions in the cell nuclei. This smaller body probably represents the remnants of a nuclear chromatone. There is a characteristic halo around the inclusion, a very sharp nuclear membrane, and a very much enlarged epithelial cell. The lumen of this tubule was filled with protogenous material forming a cast; the inclusions, as you notice, do not occur in regular, but in haphazard fashion. The lining epithelium here appears to be completely devoid of the change.

This slide shows a higher magnification of the same lesion—as a matter of fact, the very same cell, to show the striking contrast and remarkable change in the cell size. This cell must be approxi-

mately 10-12 times the size of the adjacent normal cell—cytomegaly in its purest form.

This slide presents a still higher view of these inclusions. It brings them out in greater detail and once again shows the marked contrast between the cell nucleus rendered abnormal by the presence of the inclusion—which presumably is virus—and the non-affected nucleus with its evenly dispersed chromatin and ordinary round appearance.

This is a photograph of an inter-nuclear inclusion in a tubular epithelial cell as it might be found in a urinary sediment. The cell outline is not too well brought out here and the nuclear distortion is quite evident, the distortion occurring primarily as a result of nuclear protein which is the inclusion body as it occurs in this disease. The interesting thing about the inclusions in this disease is that they occur not only in the nucleus of the cell (as we'll see in the next photograph) but also in the cytoplasm of some of these cells.

This is the cytoplasmic inclusion, again in a cell found in the urinary sediment of a similar case. The nucleus was pushed aside and in contrast to the basophilic staining cytoplasmic inclusion, or rather internuclear inclusion, the cytoplasmic inclusion is pink-staining eosinophilic, and stands out in sharp contrast to the dark staining inter-nuclear body.

The other significant point about viral infections in infants is that cytomegalic inclusion disease is not the only viral entity in which inclusion bodies can be found in the urine. This slide shows a cell obtained from the urinary sediment of a child with measles. It pictures the characteristic large giant cell as it occurs in measles with the peculiar polymorphous nucleus, and even multi-nucleation in some other cells.

Many years ago I understand from senior pathologists one of the few delights they had, was to be able to examine an appendix removed from a child, find the typical giant cell in the appendix, call the surgeon and say: tomorrow or the next day, the patient will have measles—and lo and behold, it would happen! Now thanks to Dr. Papanicolau, and some curiosity on the part of others, perhaps we can say this to the pediatrician with much less risk to the child.

This slide shows a section of the parotid gland of this child, the

inclusion body was originally referred to as a salivary gland virus. I believe this refers to the work done by Dr. Walbach in Boston in the early '30's. Being the thorough pathologist he was, he saw no reason why he should not routinely examine salivary glands in infants he autopsied, and much to his surprise, he found that approximately 30% of them had these inclusion bodies and there was no evidence of generalized or systemic disease in these infants. They died from other causes. Once again, there's a disappointing absence of inclusions in the salivary gland of this child. There is, however, a fairly striking interstitial inflammatory reaction; it occurred in fairly characteristic fashion, in that it seems to surround the ducts within the gland. Reaction in the tissue proper is entirely unremarkable.

And this is another photomicrograph of some of the renal tubules. They show a rather pronounced but early nephrotic change. The lining epithelial cells are ballioned, swollen, had a feathery appearance and not infrequently are stained with bile. This is an almost inevitable consequence of abnormal elevations of bile as it affects the kidney, namely, the occurrence of a bile nephrosis; as you probably know, this can be manifested clinically simply by a mild albuminuria or it can go the entire gamut of renal disease to the point of presenting a complete nephrotic syndrome, which this baby did not have.

This next, is a photograph of the pancreas and here we see the fairly characteristic pancreatic changes as they occur in uremia, namely the dilatation of some of the pancreatic acini and the occurrence of pink-staining inspissated material within the lumen thus formed. About 40-50% of patients dying in uremia will manifest this anatomic change. It is not pathognomonic of uremia, but when one sees it—in at least half the cases—one can guess correctly that uremia was present; then, of course, we have the renal change, the abnormal bile metabolism to substantiate the assumption in this case.

DR. FRIED: Any questions or comments?

DR. LEVY: I recently had occasion to see a case where a diagnosis had been made at a very reputable medical school of cytomegalic inclusion disease and when I saw the child, I questioned the diagnosis. I was very glad to see you show that there are things other than cytomegalic inclusion disease which will produce inclusion bodies in urinary sediment. This particular child did not have a liver and spleen, and subsequently the diagnosis was contradicted, and it was not cytomegalic inclusion disease.

Recently I had dinner with Dr. Daniels who had several cases at Bellevue. He made a point, which I think might well be taken here too, and that is that we do not get these cytoplasmic inclusions without also having inter-nuclear occlusions. There's only one thing that I'm not clear about and possibly you can answer it. With a known case of cytomegalic inclusion disease, what's the prognosis for the future, morbidity or survival?

DR. BUCALO: As far as I can gather from the literature, there are a variety of forms which this disease can take; when it occurs as it did in this baby, in the perinatal period with the full blown manifestations that we had here, I think it's generally agreed that the prognosis is nil. When there is hepatosplenomegaly, bleeding tendencies, the severe jaundice that this child had, the extramedullary hematopoesis that we saw in this child, it's almost hopeless. If it occurs in an older child, still during the infancy period, then the prognosis perhaps can be designated as guarded but not hopeless. A number of survivals, long-term survivals, have been reported in the literature with this disease as it occurs in the older child, even as young as 2, 3, 4 months of age. There is still a later form of the disease that occurs in children a year of age or older, but in this form, it does not manifest itself hematologically or with hepato-splenomegaly. These children, I understand, will present primarily symptoms referable to the respiratory tract and/or the gastrointestinal tract. I don't know of any case report that has indicated a diagnosis has been made in these children. The few that have come to autopsy in this older age group have manifested pulmonary inclusions, and inclusions in the g.i. tract, as well as other organs. Cases that appeared similar on clinical grounds, but in which, as far as I can recall, the diagnosis was not made histologically or pathologically, have gone on to recovery. So that it would appear the prognosis depends on the age at which it occurs and the type of manifestation it gives us, whether the hematopoetic apparatus is the primary clinical manifestation or not. I guess that's about it, but it is not invariably fatal in the older child. It also occurs in adults, apparently, as a meaningless and interesting and incidental finding at autopsy in patients dying with other diseases (Hodgkin's disease, for example). Occasionally, in a terminal patient when he comes to autopsy, there will be inclusion bodies which are not believed to be related to the underlying tumor. I should say that Dr. Edith Potter has been very much interested in this disease for many years, as she has in many

other diseases, and she feels quite strongly that the organism, which has been isolated and grown in tissue culture, is transmitted transplacentally. Her evidence is the relative ease in doing this in lower animals: hamsters, guinea pigs, hogs, for example—the inoculation of chick embryos with virus material is old hat now—and as it occurs in the human we know that inter-nuclear inclusions are found in stillborn fetus, so that the evidence for the human for trans-placental transmission is strong although indirect. The odd thing about it apparently is that it does not result in congenital malformations.

QUESTION: Have they done any work on the mother? If it comes through trans-placental transfer you would expect her to show—

DR. BUCALO: I don't recall any such studies. I would guess that the finding of inclusion bodies in urinary sediment probably is a reflection of viremia rather than the occurrence of inclusion bodies in the tubular epithelial cells necessarily because of finding it in other virus infections in children. Anything that will produce an xanthema in a child theoretically can give rise to the finding of inclusion bodies, and as far as I'm aware, we don't have a comparable renal lesion in chickenpox or measles such as we have here, so I suspect it may just reflect viremia.

QUESTION: I had a case of my own about two years ago at Babylon Hospital and that child had all the characteristics of leukemia in a newborn and it was so signed out.

It was not until we got the autopsy report that we found inclusion body disease in almost every organ in the body, yet nobody considered it as a diagnosis until the autopsy report.

DR. BUCALO: I'm not surprised to hear that. Dr. Potter in a recent paper discussing the transplacental passage of this agent mentions in passing a pathologist who referred to her a case which he was convinced was erythroblastosis fetalis. It seemed a short time prior to that Dr. Potter had made the statement that erythroblastosis on the basis of an ABO incompatibility, if it occurs, is very mild indeed and stands in striking contrast to the problems one has with Rh incompatibility. While it appears that this baby did have some degree of ABO incompatibility and died of jaundice and the pathologist found a great deal of extra-medullary hematopoesis, he sent the case to Dr. Potter and said "see, you're wrong". She simply looked at the kidneys and sent them back to

him and said "see *you* were wrong; you missed these inclusion bodies". So, it can resemble a number of diseases very closely.

QUESTION: Isn't the presence of inclusion bodies pathognomonic—inclusion cell disease?

DR. BUCALO: The diagnosis is made on the characteristic finding such as occurred in the kidney of this child. The only odd thing about this case is that they occurred only in the kidney.

QUESTION: Is this unusual?

DR. BUCALO: I'm not aware of it. There's nothing characteristic about the inclusion bodies. The thing that is characteristic is the *generalized* aspect of the inclusions. I think other viruses have a tropism that's more pronounced than this virus.

DR. FRIED: I wonder if Dr. Schorr would discuss the immunological aspects?

DR. SCHORR: Well, there isn't very much that one could comment on, Dr. Fried. There is no explanation for cytomegalic inclusion disease. I might say splenic enlargement in this disease is not very great. As a matter of fact splenomegaly is very unusual in cytomegalic inclusion disease, although the opposite is considered frequently so, we definitely have seen hyposplenomegaly. This child had a little bit more than usual. As far as the anemia is concerned, workers in hemolysis have suggested that in the virus diseases causing viremia, the virus attaches itself to the red cell, and makes these cells act as they do. We don't know and this is the only explanation we've had thus far. If you could produce antibodies then you could learn the direct effect.

QUESTION: Would you say the virus can be grown and identified?

DR. BUCALO: Yes, it has been grown in cultures. We sent the kidneys in this case to the Department of Health to isolate the virus, and they were unsuccessful.

DR. FRIED: Dr. Schorr?

DR. SCHORR: There are serological tests now for cytomegalic inclusion disease. Last year at one of the Pediatric meetings, it was pointed out that there were three types, three serologically different viruses, in cytomegalic inclusion disease. Like any other virus once you start playing around, they increase in number. I

don't know whether one can get a characteristic pattern in mother and infant in this disease, such as one gets with toxoplasmosis.

DR. FRIED: Thank you Dr. Bucalo. The last case is both unusual and confusing. It's an unusual case of rheumatic fever. It will be presented by Dr. Malgieri.

RHEUMATIC FEVER

DR. MALGIERI: This is a 13-year old white boy who was admitted to the hospital with a history which began the day previous to admission at approximately 5 p.m. After playing a vigorous game of basketball, he returned home feeling nauseated and vomited one time. Three hours later he developed excruciating pain in the left flank which radiated to the left groin. He was brought to the emergency room of another hospital where a flat plate of the abdomen was taken and a urinalysis performed. These were negative. The child was sent home with a sleeping pill, taken at bed time. He spent an uneventful night and in the morning complained of pain of severe nature in the left flank again. However, at this time the pain radiated to his left shoulder. He was seen by his private physician who advised hospitalization. No urinary symptoms. The night previous he had passed his urine twice. The past history disclosed that he had been admitted to Misericordia Hospital previously with a history of recurrent upper abdominal and peri-umbilical pain accompanied by nausea, vomiting and diarrhea, but no fever. These attacks of pain have been recurrent over a period of six years, unrelieved by the usual anti-spasmodic medications. While in the hospital, he had urine and stool examinations which were reported negative, a G.I. series was also reported as negative, and blood count reported as negative, and still no fever. He was discharged with a diagnosis of enterospasm due to diet. During this first admission no EKG was performed. Perusal of his chart showed a cardiac rate between 52 and 90 with no irregularities noted. The family history was essentially negative.

Physical examination showed a somewhat underweight boy of 13, who was not in acute distress, alert, cooperative and oriented. Temperature was 100 degrees, respiratory rate 24 and regular, pulse rate was 56 and regular.

Examination of the head, neck and chest was essentially negative. The heart was not enlarged. Sinus bradycardia was a rate of 56. There were no murmurs. A-2 was greater than P-2, and the blood pressure was 110/60. The abdomen was flat. Liver and spleen

were not enlarged. Areas of rigidity and muscular defect were not present. No rebound tenderness was noted. No masses were felt. There was deep tenderness over the left flank with positive Murphy. Neuromuscular examination was normal. There was no inguinal lymph adenopathy. The patent started to spike a temperature which was intermittent with varying fluctuations to 103 degrees. The patient's pain recurred on the second day. At this time a perinephritic abscess was considered as a possibility.

On the third hospital day the patient's creatinin was .6, creatin 2.8, and on the 9th hospital day creatinin was 54, and creatin 32.5.

Heterophile agglutinations were negative. The Watson test for porphyrins in the urine was reported as positive and his stool guaiac was 2 plus. There were no ova or parasites. Repeated blood cultures were negative. X-ray report: flat of abdomen, on admission, negative. The chest was reported as normal. Intravenous pyelograms were reported as normal. Repeat x-ray of the abdomen was done six days after admission and showed no change. The chest showed no change 6 days after admission.

On the fourteenth day of admission, the chest showed some exaggerated outline of the hilus suggesting a respiratory infection.

Cardiograph done on the fourth day after admission showed irregular sinus rhythm with frequent premature mild ventricular extrasystoles. T-wave was inverted in the AVL. P-interval was 16, QRS .06, irregular and ventricular rates were 85. The cardiograph on the seventh day after admission disclosed wandering pacemaker, with some areas of nodal rhythm. The T-wave was variable, preceding the QRS in some leads, and incorporated in the ST segments in other leads. Repeated cardiographs over the next two weeks showed ST and T segments.

Before discharge the auricular rate was 54, P-R interval of 12, QRS .06, sinus bradycardia.

DR. FRIED: This case will be discussed by Dr. Cesare Cucci, Assistant Pediatric Cardiologist at Misericordia Hospital.

DR. CUCCI: I also wish to thank you gentlemen, for the privilege granted me to come and discuss this case here tonight.

The physical examination and physical findings changed a little every time I saw the boy. At the time I saw him, I hesitated for a few days and only after some hesitation and after several medical

and surgical conditions had been ruled out by the attending pediatrician, surgeons, and a pediatric hematologist, with some hesitation, I diagnosed rheumatic fever on the following grounds: the low-grade fever, a generalized lymph adenopathy, a vague, indefinite abdominal pain, a high white count, a high sedimentation rate, a moderately elevated antistreptolysin O titre, and above all upon a fast changing variety of cardiac arrhythmias.

It would be nice to project some diagrams of some of the electrocardiographic pattern this child developed during the illness. I don't have the electrographic tracings; however, I copied some of them—the most significant.

The first one—this may not be the first but the chronological order doesn't matter—the child developed an AV block. I drew on a lantern slide the sinus node, the atria and the ventricle.

This is a second degree AV block which starts at a stimulus which is forming in the sinus goes laterally and eventually reaches the ventricle. However, successively one stimulus is blocked and nothing goes to activate the ventricle.

Later on, this child developed another variety of second degree AV block, the variety that goes under the name of "Wachenbach" where the P-R interval is progressively longer until finally one stimulus is completely blocked at the level of the A-V junction. Then again, the next stimulus from the sinus builds out to the atria and then down to the ventricle in a normal fashion and again the P-R is prolonged in the next even in a more disturbed, and eventually another blocked stimulus.

Later, this child developed a third degree AV block whereby no stimuli actually reached the ventricles, and the ventricles contracted with nodal rhythm. The child then developed an AV dissociation with an interference, still there is fundamentally a complete block at the level of the atria. However, now the ventricles beat much faster than the usual nodal rhythm would allow them to beat; however, once in a while it does happen that one stimulus goes down to the atria and to the ventricle in the normal fashion.

On superficial analysis of the salient features of this case, a low-grade fever, abdominal pain, high white counts, sedimentation rates, and these peculiar arrhythmias, it did appear that we might have enough here to make a diagnosis of rheumatic fever as a clinical diagnosis. There are no pathognomonic signs of course, and we

are all aware that for each typical case of polyarthritis, and massive carditis, there is a more subtle and insidious clinical picture. Abdominal pain occurs not infrequently in rheumatic fever.

During the first days, we started this child, still without a diagnosis but with a strong suspicion, on high doses of aspirin around the clock. In a few days the abdominal pain subsided, temperature came down to normal. The white count and the sedimentation rate dropped to normal levels, and at last the electrocardiogram showed a regular sinus rhythm with a normal P-R interval. This response was interpreted as strengthening the suspicion for rheumatic fever; in fact is not a course of salicylates an indirect and often performed diagnostic test for this condition?

Actually today, one year later, I feel very dissatisfied with the diagnosis. I shall not indulge in a critical appraisal of this case; that would be vain today. It is, I suppose, obvious to all, that of presenting signs and symptoms only two deserve any particular mention: the moderately elevated antistreptolysin titre, which is not reported there, it was 625 Todd units, and the arrhythmias.

On the third or fourth day after admission the titre was 625 units. However, at the time of discharge, two weeks later, the titre remained at the same level. This plateau type of curve should have alerted us. This is very unusual after a recent streptococcal infection, the titre should have continued to rise. As far as the arrhythmias, there is no doubt but this child had a mild carditis, mild perhaps but sufficient to impair conduction of the stimulus from the atria to the ventricle. However, not all carditis is rheumatic, many are from fungi, viruses.

I said before it would be mere speculation to try to rediagnose this case tonight, but allow me, purely for discussion's sake, to mention that a few months ago, I had the good fortune to see another child, a 6 year old girl, with a frighteningly similar picture to this boy: vague abdomen pain, nausea, vomiting, peculiar arrhythmias, and a low-grade fever. The girl's mother had just recovered from an illness diagnosed by her family physician as grippe, but she was still complaining of shooting pain beneath her right breast. We did a compliment fixation test for Coxsackie virus on the girl's and the Mother's blood. The test came back positive. The child had a Coxsackie mild carditis, and her mother had recovered from a Coxsackie pleurodynia. I wonder whether our boy, the case we are discussing tonight, could not also have had a Coxsackie mild carditis.

DR. FRIED: Thank you very much. Dr. Schorr, would you like to comment on this case, I think you saw him.

DR. SCHORR: Yes, I saw him about an hour or two before Dr. Cucci did and at the time that I was called, I was told that the surgeons and pediatricians were considering a ruptured spleen, or possibly a spleen that was enlarging from infection. When I got there, the boy was rather poor. He was running a high fever. After I went out and went back to check, I was amazed to find the boy running all over the place, and I headed down to the dining-room where Dr. Casey was waiting. I said, "last time I heard a pediatrician and a surgeon argue about a case like this, it turned out to be rheumatic fever" so perhaps that's how Dr. Cucci got his impression (laughter). One of the problems did come up when we made the diagnosis and I think it's still worthwhile talking about tonight. When you have a child and suspect rheumatic fever—and we had the right to suspect it seriously here—you are inclined to tie the label on for two reasons: (a) because it gives you a diagnosis to hang your hat on, and (b) because it gives you a form of prophylactic therapy that may save you trouble later on, and there are certain advantages today in labeling a child rheumatic, which were not present 20 years ago, as well as disadvantages. I think prophylactic antibiotics play a very worthwhile role in conjunction with recurrent attacks.

QUESTION: Just a short question. If you felt the child had rheumatic fever, would you give him prophylactic therapy?

DR. CUCCI: I have been treating children with penicillin for many years.

QUESTION: Within the past year, we had occasion to see two children who puzzled us considerably: one was an 18-month old child who came to Harlem Hospital with tremendous enlargement of the heart. There were no murmurs or other signs. The child ran a temperature. Blood pressure was normal. Urine was normal, and we were at a complete loss for diagnosis. I think we did do a complement fixation test. We were at a complete loss as to the diagnosis. He was extremely sick, dyspneic, orthopnic, had enlargement of the liver. Dr. White saw it and followed the child, cardiologists saw it, nobody could make a diagnosis. Eventually, the child recovered and is entirely well.

Then we had another child who came in who had been watched at Morrisania with a general heart condition, congenital in nature.

She was supposed to have a work up but somehow or other it was never done. She came to Harlem very sick, orthopneic and in pain. This child got everything. The cadiologist thought that she had rheumatic fever, had an enlarged heart with systolic. We did everything. We gave steroids, large doses of penicillin. The child was running an up and down temperature, and we thought she might have an acute endocarditis. The child died.

At autopsy the findings were extremely minimal. There were some minimal lesions along the cuspidal valves. We never got the sections of the muscle, but both of these children were terrific problems, and I was just wondering whether they don't fit into the picture of so-called viral myocarditis.

DR. CUCCI: Coxsackie myocarditis is becoming more and more easy to diagnose and the medals here go to the pathologists rather than the clinicians. This is found not only in this age group but sometimes in senile conditions which often are thought to be chronic myocarditis of unknown etiology. Coxsackie can be responsible for some, and these may be serious in newborns.

DR. ALASCO: Dr. Cucci brought out the point of the response of rheumatic fever to salicylates. I do not want to take up a controversal point at this time; however, there are many schools of thought in the use of steroids and the use of salicylates in treating rheumatic fever, having made a bedside diagnosis of rheumatic fever, using steroids in the presence of a viral infection, I am aware that sometimes steroids are not possible; however, there are many authorities who say just the opposite. One study which is going on has not shown any advantage of steroids over salicylates. By this I don't mean to say I don't use steroids in rheumatic fever—I do. Now, what effect steroids alone would have had on this boy had he had endocarditis, I don't know.

DR. FRIED: On behalf of Misericordia Hospital, I want to thank the Bronx Pediatric Society for inviting us here.

DR. GOLDFARB: I want to thank Dr. Casey, Dr. Fried, and the staff of the Misericordia Hospital for this very interesting set of cases and I wish to thank the discussors for this very erudite and elucidating discussion.

EPILEPSY AND RELATED DISORDERS. William G. Lennox and Margaret A. Lennox. Two volumes. Little, Brown & Company, Boston, 1960. $13.50.

THIS BOOK is an extraordinary achievement. The senior author —who, as early as 1934, recognized the importance of H. Berger's discovery published only one year before, and obtained, along with Gibbs and other associates a characteristic electroencephalogram in patients subject to *petit mal*—reviews and summarizes his life's work. All aspects of the problems of epilepsy—history, pathogenesis, causation, clinical manifestations, therapy, sociologic implications and statistics—are presented by a great, warm-hearted physician who also possesses a fine cultural background. The facts accumulated in these two volumes will remain for a long time to come an abundant source of information, not to say material for future research.

Of all systems of the body, the brain is most nearly cyclic in function. "Epilepsy is merely a disturbance of the normal rhythm of the electrical potentials of the brain; in the brain, paroxysmal dysrhythmia spells epilepsy." "Epilepsy is an anarchy of cell function, just as cancer is an anarchy of cell growth." The central symptom of a seizure is, according to the authors, not a muscular movement, but loss of consciousness. There is no typical epileptic fit. "The severity ranges from muscular rigidity and jerking, which can be both brief and mild, to a convulsion of demoniacal violence." The authors recall R. Bright's (1831) belief that a person could be epileptic, even if *grand mal* had never been observed.

Although the initiator of EEG research in epilepsy, Dr. Lennox stressed as follows: "We must accept the fact that the attempt to correlate symptoms with interictal EEG findings is oftentimes not possible."

Electroencephalographic studies indicated that "seizure discharges were too fast, too brief, and too variable in locus to be explained by a relatively slow vasomotor mechanism. Cerebral circulatory changes are interesting and important phenomena in epilepsy, but in general are passive rather than active features in a seizure". Thus, the theory of vasospasm is viewed with skepticism. The authors assumed that genetic causes predominated in the etiology of epilepsy. "Transmission of a predisposition to seizures is a fact." Nevertheless, "inheritance is less important in epilepsy than in many other common diseases, for which the wisdom of marriage is never questioned. Both doctors and the public have overlooked this important fact."

Environmental factors are also considered thoroughly by the authors. A considerable part of the book deals with cases in which birth injury occurred in children born full-term or prematurely. Particularly instructive, and disheartening, are cases described by the authors, in which intentionally delayed delivery caused epilepsy and mental defects.

Nielsen and Courville's suggestion (1951) that one-half of all cases of idiopathic epilepsy are the result of birth injury or asphyxia, the rest being due to a variety of forms of cerebral damage, is commented on by the authors as follows: "This conception is far different from our own, but is given support by the study of Lilienfeld and Pasamanick (1954)." Also, the authors quote the conclusion of Lilienfeld and Pasamanick's paper which raises doubts as to the genetic basis of convulsive disorders.

In assessing the influence of epilepsy on the personality, the authors advise that "our view must include the imbecile, the man of genius, and the world of epileptics who lie between". It is impossible to consider, or even to list, here all the results and statements of the authors concerning clinical classification and therapy in epilepsy, although they are of great importance, being based on rich experience and documentation.

One of the two concluding sentences is the following: "In this book the reader has traveled with us a journey which has been extensive, winding, and at times, wearisome . . ." Yes, the "journey" *was* "winding" and in general, wearisome, since this unique and valuable material is often presented in a rather chaotic manner, leading to discursiveness, repetitions and sometimes, loss of perspective. However, we would not wish to forfeit even a sentence of the text, although we feel it might be better organized and its structure more balanced. This is a great monument . . . imposing in its significance, quality and wisdom. Nevertheless, the following words engraved by the authors will never fail to impress: *"Epilepsy is not a mysterious disease and certainly is no disgrace. Simple epilepsy, like diabetes, is a metabolic disorder. Enigma perhaps, but stigma no. It tends to get better with time rather than worse. There are effective medicines. The mind is rarely affected. A child should continue schooling, and the adult should work. Activity is an antagonist of seizures. Marriage and children are not necessarily precluded. Given social acceptance and modern medical treatment, the great majority of patients can lead normal lives."*

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